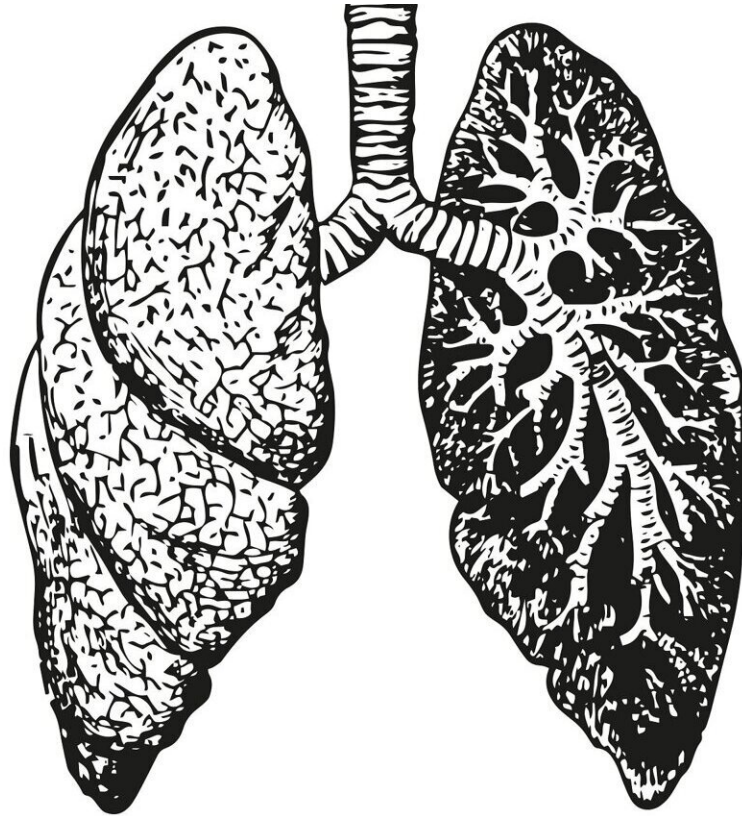


Genetic clues reveal lung cancer's next move

April 13 2023



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Knowing whether a tumor might grow or spread to other parts of a patient's body could be key to survival—and now scientists are one step closer to unlocking the ability to predict just that.

In a series of seven papers published today (Wednesday, April 12) in

Nature and *Nature Medicine*, researchers based at the Francis Crick Institute and University College London (UCL) describe how changes to cancer cells' DNA are enabling them to anticipate how those cells will behave in the future.

This includes where and when cancer will spread to other parts of the body in a process known as metastasis, which is responsible for most cancer deaths worldwide.

The findings could one day allow doctors to use a blood test to predict how a patient's cancer may grow and spread, enabling them to track it and rapidly adapt treatment in real-time. It also offers a possible route through which clinicians could analyze the disease's risk of returning following surgery.

While the research was carried out on patients with [lung cancer](#), the scientists say their findings could also be applied to other cancer types, such as [skin cancer](#) or [kidney cancer](#).

These studies are the culmination of 9 years of research from Cancer Research UK's £14 million [TRACERx study](#)—the first long-term study of how lung cancer evolves. TRACERx is a nation-wide research effort, involving more than 800 patients in clinical trials and a community of 250 investigators who based at 13 hospital sites across the U.K.

Lead researcher based at the Francis Crick Institute in London, UCL and Cancer Research UK's Chief Clinician, Professor Charles Swanton, said, "TRACERx recognizes that cancer is not static and the way we treat patients shouldn't be either.

"What makes the TRACERx project particularly powerful is that it treats tumors as ever-changing 'ecosystems' made up of diverse cancer cell populations.

"By looking at the [tumor](#) in its entirety, we can observe how these cell populations interact and even compete with one another, which is helping us to glean valuable insights into the likelihood that a tumor will return and when this might happen. We can also observe how the tumor is likely to evolve over time, spread and respond to treatment, offering hope to millions of patients in the future."

In these seven studies, researchers at the Crick and UCL followed 421 of the 842 TRACERx participants from when they were diagnosed to monitor how their tumors changed over time. The patients had [non-small cell lung cancer](#) (NSCLC), the most common type of lung cancer.

Among the major findings in the seven papers, the researchers found that:

- Tumors can be made up of many different populations of cancer cells which carry sets of genes that are constantly changing. The more diverse these tumors are, the more likely the patient's cancer will return within one year of treatment.
- Some patterns of DNA changes when observed in a patient's tumor indicate what their cancer might do next.
- These patterns could indicate to doctors which parts of a tumor might grow and spread to other parts of the body in the future.
- Blood tests could be used to monitor these changes to tumor DNA in real time, helping doctors pick up on early signs that cancer is returning or not responding to treatment.

Constant changes to cells allow tumors to thrive

Tumors are made up of different "populations" of cancer cells which all carry different genetic mutations. The more diverse these mutations are, the more that tumors can evolve and gain resistance to treatments.

The researchers found that specific patterns of genetic mutations in cell populations enable the cancer to return in a patient quicker—within one year of surgery.

These patterns of mutations also indicate whether a tumor is more likely to spread to other areas of the body beyond the lungs and chest.

Armed with this information, doctors could one day predict if someone with early-stage cancer, who should be treated successfully with surgery, may end up seeing their cancer return.

In another discovery, researchers found that the genetic diversity of cell populations within a tumor not only stems from genetic changes, but also from the way that genes are expressed.

Changes in gene expression can affect important aspects of cancer biology, including whether a tumor will return after surgery.

In this instance, the researchers suggest that doctors treating lung cancer patients could intervene early by identifying those whose cancer is most at risk of returning after surgery and following up with further treatment, to help prevent the cancer from coming back.

Identifying what leads cancer to spread

The researchers also looked more closely at how lung cancer spread in the TRACERx participants.

They identified which cells in a tumor were most likely to be responsible for a cancer spreading (metastasis) in the future because these cells were more likely to harbor certain changes in their genes. These indicate that a cell has a higher chance of leaving the tumor and moving to other parts of the body, where it then grows into a new tumor.

Metastasis is responsible for the majority of cancer deaths, so understanding which parts of the tumor are responsible for triggering this process could allow researchers to target treatments specifically to prevent cancer from spreading.

Transforming how we track people's cancers

The TRACERx scientists also investigated whether they could track changes in the tumor and features of its genetic diversity without the need for surgery or biopsies, a type of invasive medical procedure that involves taking a small sample of tissue and examining it in a lab.

By analyzing DNA released into the bloodstream from tumor cells, known as circulating tumor DNA (ctDNA), they found that the presence of ctDNA in the blood before or after surgery suggested that the patient's cancer was highly likely to return in the future.

The presence of tumor DNA in the blood isn't the only indicator that cancer might spread or come back. Researchers found that microscopic patterns created by the arrangement of tumor cells are linked with the risk of cancer returning.

Executive director of research at Cancer Research UK, Dr. Iain Foulkes, said, "A [blood test](#) that reads ctDNA could let doctors track someone's cancer in real time, allowing them to personalize treatments to that patient.

"Currently, the best option we have to monitor a patient's tumor is to extract tissue either through a biopsy or during surgery. Both are invasive and time-consuming options which give us a limited snapshot of how that tumor is behaving at a given point in time.

"Analysis of ctDNA would give us a fuller picture of how the tumor is

changing over the course of the patient's disease using minimally invasive blood tests. It would allow doctors to treat people more proactively, taking swift action to change a treatment plan that's not working."

TRACERx has already entered its next phase, known as TRACERx EVO, which will receive just under £15 million in additional funding over the next seven years to further our understanding of tumor evolution and use that knowledge to change how patients with [cancer](#) are treated.

More information: Alexander M. Frankell et al, The evolution of lung cancer and impact of subclonal selection in TRACERx, *Nature* (2023). [DOI: 10.1038/s41586-023-05783-5](https://doi.org/10.1038/s41586-023-05783-5)

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Provided by The Francis Crick Institute

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